SCIENTIFIC ABSTRACT

The long-term goal is develop a clinically effective vaccination strategy for patients with metastatic renal cell carcinoma (RCC) by using dendritic cells (DC) transfected with tumor RNA. The central hypothesis of this proposal is based on two recent discoveries that a) vaccination with RNA transfected DC elicits potent, potentially therapeutic T cell responses in human cancer patients and b) T cell mediated antitumor immunity can be enhanced to therapeutic levels through antibody-mediated elimination of regulatory T cell subsets.

We have previously shown that RNA transfected DC are remarkably effective in stimulating potent, antigen-specific T cell responses in vitro. Therefore, we have performed two clinical trials in which prostate and renal cancer patients were immunized with PSA RNA or renal tumor RNA transfected immature DC respectively. In all evaluable subjects, we not only established the safety of this approach but, more importantly, we demonstrated the bioactivity of the vaccine to induce detectable levels of PSA or renal tumor-specific T cells in the peripheral blood of study subjects after vaccination. Despite these encouraging clinical results, recent research indicates that the immature DC used in our early trials are rather suboptimal in stimulating immune responses in humans whereas fully matured DC have shown to be superior in eliciting potent and potentially therapeutic antitumor immunity. Furthermore, several studies conducted in murine and human systems have identified peripheral blood T cell subsets, which act in an immunoregulatory capacity by suppressing the function of other T cells including CD8 cytotoxic T cells. Specifically, CD4 T cells carrying the IL-2 receptor α-chain (CD25), termed regulatory T cells (T_{reg}), have shown to diminish immune responses against viruses, tumors, and self-antigens in *in vitro* and *in vivo* models. Conversely, it has been demonstrated that depletion of $CD25^+$ T_{reg} dramatically enhances antitumor immunity in conjunction with standard immunotherapy protocols. Utilizing these novel concepts, we propose to perform a clinical trial of active immunotherapy in which mature, tumor RNA transfected DC will be administered to patients with metastatic renal cell carcinoma (RCC). Moreover, we will seek to gain preliminary evidence as to whether or not $CD25^+$ T_{reg} depletion prior to immunization represents a superior strategy to elicit potent antitumor responses in cancer patients when compared to patients receiving the vaccine alone. With this trial, we propose to further extend our prior clinical experience with RNA transfected DC in the treatment of human cancer with the goal of stimulating potentially therapeutic, tumor-specific T cell responses in metastatic renal cell patients.

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